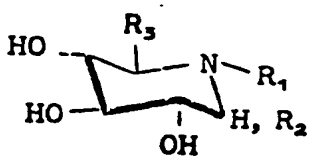
The present invention relates to new derivatives of 3,4,5-trihydroxypiperidine, several processes for their preparation and their use as medicaments, in particular as agents against diabetes, hyperlipaemia and adiposity, and in animal nutrition, for influencing the lean meat/fat ratio in favour of the proportion of lean meat.

The new derivatives can be represented by formula I



I

in which

R_1 represents H or an optionally substituted, straight-chain, branched or cyclic saturated or unsaturated aliphatic hydrocarbon radical or an optionally substituted aromatic or heterocyclic radical,

R_2 denotes -H, -OH, -OR', -SH, -SR', $-NH_2$, -NHR', $-N<^{R'}_{R''}$, NH_2CH_2-, NHR'-CH_2-, NR'R''-CH_2-, -COOH, -COOR', HO-CH_2-, R'CO-$NHCH_2$-, R'CO-NR''CH_2-, R'SO_2NHCH_2-, R'SO_2-NR''CH_2-, $-SO_3H$, -CN, $-CONH_2$, -CONHR' or -CONR'R'' and

R_3 can have the meaning given for R_1, but preferably represents -H, $-CH_3$, $-CH_2OH$, $-CH_2-NH_2$, NHR'-CH_2-, NR'R''-CH_2-, R'CONH-CH_2-, R'CO-NR''CH_2-, Hal-CH_2-, R'O-CH_2-, R'$COOCH_2$-, R'SO_2O-CH_2-, R'SO_2NHCH_2-, R'SO_2-NR''CH_2-, R'NH-CO-NH-CH_2-, R'NH-CS-NH-CH_2-, R'O-CO-NH-CH_2-, -CN, -COOH, -COOR', $-CONH_2$, -CONHR' or -CONR'R'',

wherein

R' and R'' can have the meanings given above for R_1,

and wherein

R_1, in the case where R_3 = $-CH_2OH$ and R_2 = H or OH, is an optionally substituted, straight-chain, branched or cyclic saturated or unsaturated aliphatic hydrocarbon radical or an optionally substituted aromatic or heterocyclic radical, that is to say that R_1 is not H; and

R_1, in the case where R_3 = H and R_2 = H, OH, SO_3H, -CN and CH_2-NH_2, is an optionally substituted, straight-chain, branched or cyclic saturated or unsaturated aliphatic hydrocarbon radical or an optionally substituted aromatic or heterocyclic radical, that is to say that R_1 is not H; and

R_1, in the case where R_3 = $-CH_2-NH_2$ and R_2 = OH, is an optionally substituted, straight-chain, branched or cyclic saturated or unsaturated aliphatic hydrocarbon radical or an optionally substituted aromatic or heterocyclic radical, that is to say that R_1 is not H.

R_1, R' and R'' preferably denote an alkyl radical with 1 to 30, in particular 1 to 18, C atoms, an alkenyl radical or alkinyl radical with 2 to 18, in particular 3 to 10, C atoms, a monocyclic, bicyclic or tricyclic radical with 3 to 10 C atoms, which can be saturated, mono-unsaturated or di-unsaturated, an aryl radical with 6 or 10 C atoms, or a heterocyclic radical with 3 to 8, in particular 3 to 6, ring members which can contain 1, 2, 3 or 4 hetero-atoms, in particular N, O or S, and to which a benzene ring or a further heterocyclic ring of the type mentioned can be fused, it being possible for the radicals mentioned to carry 1 to 5, in particular 1, 2 or 3, substituents.

Examples which may be mentioned of substituents for alkyl are: hydroxyl, and alkoxy with preferably 1 to 4 carbon atoms, in particular methoxy and ethoxy; acyloxy, the acyl

radical being derived from aliphatic carboxylic acids with 1 to 7 C atoms, aromatic carboxylic acids, in particular phenylcarboxylic acids, which can be substituted in the phenyl radical by -OH, -halogen, in particular F, Cl or Br, C_1-C_4-alkyl, C_1-C_4-alkoxy, nitro and/or amino, or heterocyclic carboxylic acids which are derived from 5-membered or 6-membered heterocyclic compounds which contain 1 to 3 hetero-atoms (N, O or S) and can be substituted in the heterocyclic ring by C_1-C_4-alkyl, chlorine, bromine or amino; amino, monoalkylamino and dialkylamino with preferably 1 to 4 carbon atoms per alkyl radical, in particular monomethylamino, monoethylamino, dimethylamino and diethylamino, and monoacylamino, the acyl radical being derived from aliphatic carboxylic acids with 1 to 7 C atoms, aromatic carboxylic acids, in particular phenylcarboxylic acids, which can be substituted in the phenyl radical by -OH, -halogen, in particular F, Cl or Br, C_1-C_4-alkyl, C_1-C_4-alkoxy, nitro and/or amino, or heterocyclic carboxylic acids which are derived from 5-membered or 6-membered heterocyclic compounds which contain 1 to 3 hetero-atoms (N, O or S) and can be substituted in the heterocyclic ring by C_1-C_4-alkyl, chlorine, bromine or amino; mercapto, and alkylthio with preferably 1 to 4 carbon atoms, in particular methylthio and ethylthio; halogen, preferably fluorine, chlorine and bromine; alkylcarbonyl with preferably 1 to 4 carbon atoms in the alkyl radical; carboxyl, nitro, cyano, the aldehyde group and the sulphonic acid group; and heterocyclic radicals of the abovementioned type, and also, in particular, heterocyclic radicals which are derived from sugars, preferentially from hexoses or pentoses, which can be bonded to the alkyl radical direct via a ring atom or via an -O-, -S- or -NH- bridge.

Examples of heterocyclic substituents of the alkyl

radicals are: phthalimido, pyridyl, thienyl, furyl, isoxazolyl, thiazolyl, glucopyranosyl, ribofuranosyl, oxiranyl and the like. Further suitable substituents of the alkyl radicals are aromatic radicals, such as naphthyl and in particular phenyl, which can carry one or more, preferably 1 to 3, identical or different substituents from the series -OH, $-NH_2$, C_1-C_4-alkyl-NH-, C_1-C_4-dialkyl-N-, C_1-C_4-alkoxy, NO_2, -CN, -COOH, -COO-alkyl (C_1-C_4), C_1-C_6-alkyl, halogen, in particular fluorine, chlorine or bromine, C_1-C_4-alkylthio, -SH, C_1-C_4-alkylsulphonyl, $-SO_3H$, $-SO_2-NH_2$ and $-SO_2$-NH-alkyl (C_1-C_4).

The alkyl radical can also carry a monocyclic, bicyclic or tricyclic substituent with preferably 3 to 10 carbon atoms, which in turn can be substituted by hydroxyl, amino, halogen, in particular fluorine, chlorine or bromine, or -COOH.

The alkyl radical preferably carries substituents such as hydroxyl, alkoxy with 1 to 4 carbon atoms, mercapto, alkylthio with 1 to 4 carbon atoms, halogen, nitro, amino, monoalkylamino with 1 to 4 C atoms and acylamino, the acyl radical being derived from aliphatic carboxylic acids with 1 to 6 C atoms.

Possible substituents for the cyclic monocyclic, bicyclic or tricyclic radicals R_1, R' and R'' are the substituents given for the alkyl radicals.

The aryl radicals can carry one or more, preferably 1 to 3, identical or different substituents. Examples of substituents which may be mentioned are: alkyl with 1 to 10 C atoms, which in turn can again be substituted, for example by chlorine, nitro or cyano; optionally substituted alkenyl radicals with 1 to 10 carbon atoms; hydroxyl, alkoxy with preferably 1 to 4 carbon atoms; amino, and monoalkylamino and dialkylamino with preferably 1 to 4 carbon atoms per alkyl

radical; mercapto, and alkylthio with preferably 1 to 4 carbon atoms; carboxyl, carbalkoxy with preferably 1 to 4 carbon atoms, the sulphonic acid group, alkylsulphonyl with preferably 1 to 4 carbon atoms and arylsulphonyl, preferably phenylsulphonyl; aminosulphonylsulphonyl, and alkylaminosulphonyl and dialkylaminosulphonyl with 1 to 4 carbon atoms per alkyl group, preferably methylaminosulphonyl and dimethylaminosulphonyl; nitro, cyano or the aldehyde group; alkylcarbonylamino with preferably 1 to 4 carbon atoms; and alkylcarbonyl with 1 to 4 carbon atoms, benzoyl, benzylcarbonyl and phenylethylcarbonyl, it being possible for the last-mentioned alkyl, phenyl, benzyl and phenylethyl radicals in turn to be again substituted, for example by chlorine, nitro or hydroxyl.

The heterocyclic radicals R_1 are preferably derived from hetero-paraffinic, hetero-aromatic or hetero-olefinic 5-membered or 6-membered rings with preferably 1 to 3 identical or different hetero-atoms. The hetero-atoms are oxygen, sulphur or nitrogen. These ring systems can carry further substituents, such as, for example, hydroxyl, amino or C_1-C_4-alkyl groups, or benzene nuclei or other, preferably 6-membered, heterocyclic rings of the type mentioned can be fused to them.

Particularly preferred heterocyclic radicals are derived, for example, from furane, pyrane, pyrrolidine, piperidine, pyrazole, imidazole, pyrimidine, pyridazine, pyrazine, triazine, pyrrole, pyridine, benzimidazole, quinoline, isoquinoline or purine.

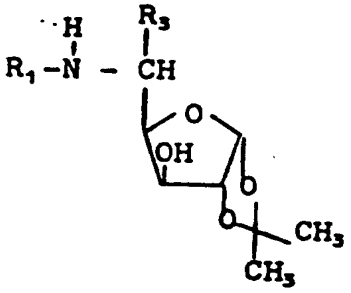
In the compounds of the formula I, R_2 preferably represents -H, -OH, $-SO_3H$, -CN, $-CH_2NH_2$, $-CH_2NH-(C_1-C_6\text{-alkyl})$ or $-CH_2NH-\overset{\overset{O}{\|}}{C}-(C_1-C_6\text{-alkyl})$. R_2 very particularly preferably represents -H, $-SO_3H$ or -CN.

R_3 preferably represents hydrogen, $-CH_2OH$, $-CH_3$, $-CH_2NH_2$, $-CH_2NH-(C_1-C_6\text{-alkyl})$ or $-CH_2NH-\overset{\overset{O}{\|}}{C}-(C_1-C_6\text{-alkyl})$.

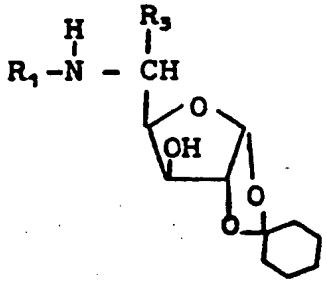
However, R_3 very particularly preferably represents $-CH_2OH$.

It has been found that the new compounds of the formula I are potent inhibitors for α-glucosidases, in particular for disaccharidases. The new compounds are thus valuable agents for influencing a number of metabolism processes and thus enrich the range of medicaments. Compared with 2-hydroxymethyl-3,4,5-trihydroxypiperidine, which is known from DT-OS (German Published Specification) 2,656,602, the new compounds have advantageous therapeutic properties.

It has also been found that compounds of the formula I are obtained when, in compounds of the formula II or IIa



II



II a

in which

R_1 and R_3 have the meaning indicated above,

the isopropylidene or cyclohexylidene protective group is removed by careful acid hydrolysis, it sometimes being appropriate to isolate the compounds of the formula I in the form of adducts of sulphurous acid or of hydrocyanic acid (R_2 = SO_3H or CN). The compounds of the formula I in which R_2 = OH are liberated from the bisulphite addition products by treatment with bases, preferably alkaline earth metal hydroxides, such as $Ca(OH)_2$ or $Sr(OH)_2$, but in particular $Ba(OH)_2$. The

compounds of the form I in which R_2 = H are obtained from compounds of the formula I in which R_2 = OH by reaction with hydrogen donor reducing agents, such as, for example, $NaBH_4$.

Furthermore, it has been found that compounds of the formula I are obtained when the compounds of the formula I in which R_2 = OH are reacted with hydrocyanic acid in a manner which is in itself known to give compounds of the formula I in which R_2 = CN, and compounds in which R_2 = $-CH_2NH_2$ are optionally obtained from these products by catalytic hydrogenation of the nitrile group, and the amino group is optionally acylated, alkylated or sulphonylated in a manner which is in itself known to give compounds in which R_2 = $R'CONCH_2-$, $R'CONR''CH_2-$, $NHR'-CH_2-$, $NR'R''-CH_2-$ or $R'SO_2NHCH_2-$.

The compounds of the formula I in which R_2 is -OR', -SH, -SR', $-NH_2$, -NHR' or -NR'R'' can be obtained by reacting compounds of the formula I in which R_2 = -OH with alcohols (R'OH), H_2S, mercaptans (R'SH), ammonia or amines (H_2NR' or HNR'R'') in a manner which is in itself known.

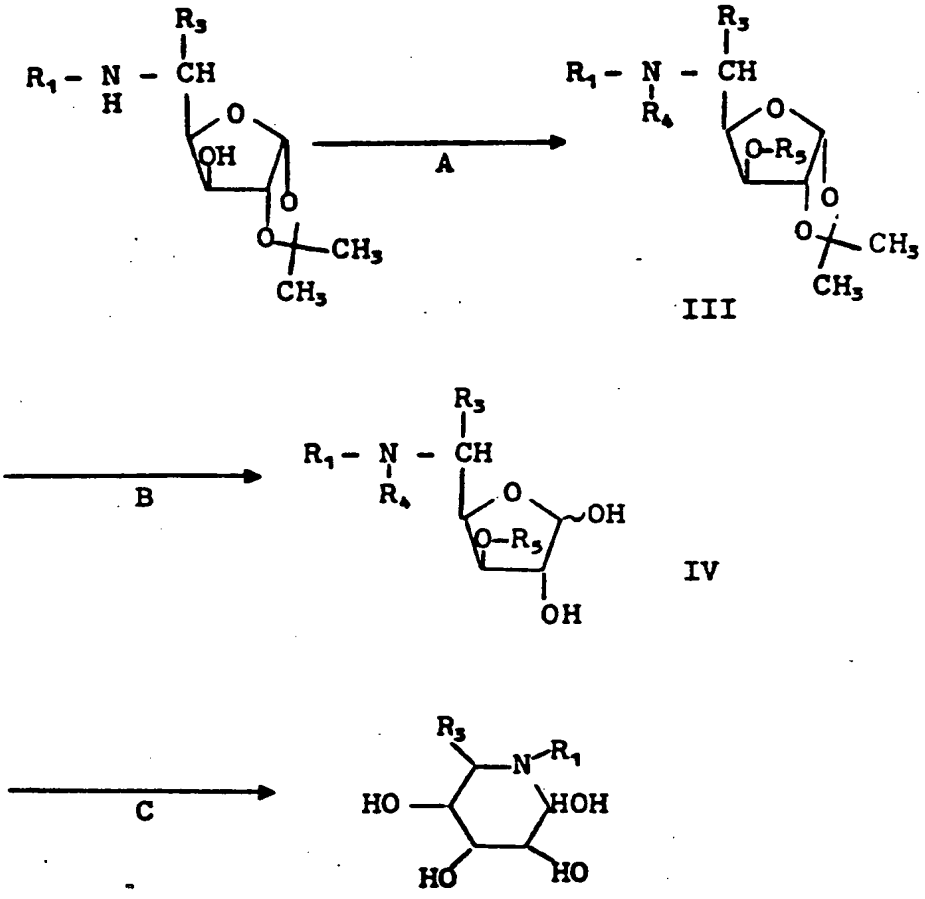
The compounds of the formula I in which R_2 is -COOH are obtained by hydrolysing compounds of the formula I in which R_2 = -CN in a manner which is in itself known.

In a manner which is in itself known, compounds of the formula I in which R_2 = -COOR' can be obtained from the resulting carboxylic acids by reaction with alcohols (R'OH), and compounds of the formula I in which R_2 = -CONHR' or -CONR'R'' or $-CONH_2$ can be obtained by aminolysis of the esters with NH_3, $R'NH_2$ or R'R''NH.

Compounds of the formula I in which R_2 = -OH can also be obtained when compounds of the formula II are reacted with trifluoroacetic anhydride in a reaction step A to give compounds of the formula III, the isopropylidene protective group is

then split off by acid hydrolysis in reaction step B and the trifluoroacetyl group in the compound IV is subsequently removed in a neutral to alkaline reaction medium in step C.

The reaction sequence indicated can be illustrated as follows:



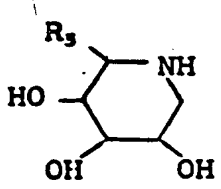
In the formulae,

R_4 represents trifluoroacetyl and

R_5 represents trifluoroacetyl or hydrogen.

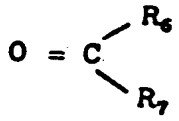
This reaction sequence can be transferred analogously to compounds of the formula IIa.

It has also been found that compounds of the formula I in which R_2 = H are obtained when compounds of the formula V



V

are reacted with carbonyl compounds of the formula VI



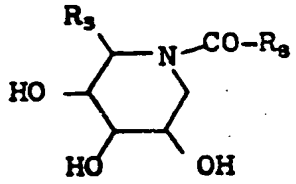
VI

in which

R_6 and R_7 either have H or have the meaning given for R_1 or are members of an alicyclic or heterocyclic ring,

in the presence of a hydrogen donor reducing agent.

Compounds of the formula I in which R_2 = H are furthermore obtained when amides of the formula VII

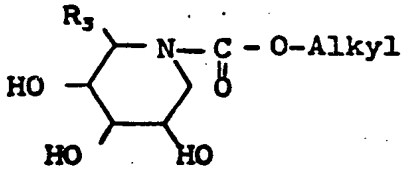


VII

in which

R_8 is either H or has the meaning given for R_1,

or carbamates of the formula VIII



VIII

- optionally also derivatives of these compounds which are provided with hydroxyl-protective groups - are reduced to amines with an amide-reducing agent.

A further process for the preparation of compounds of the formula I in which R_2 = H consists in reacting compounds

of the formula V with reactive alkylating agents of the formula IX

$$Z - R_1 \qquad \text{IX}$$

wherein

R_1 has the meaning of alkyl indicated above and

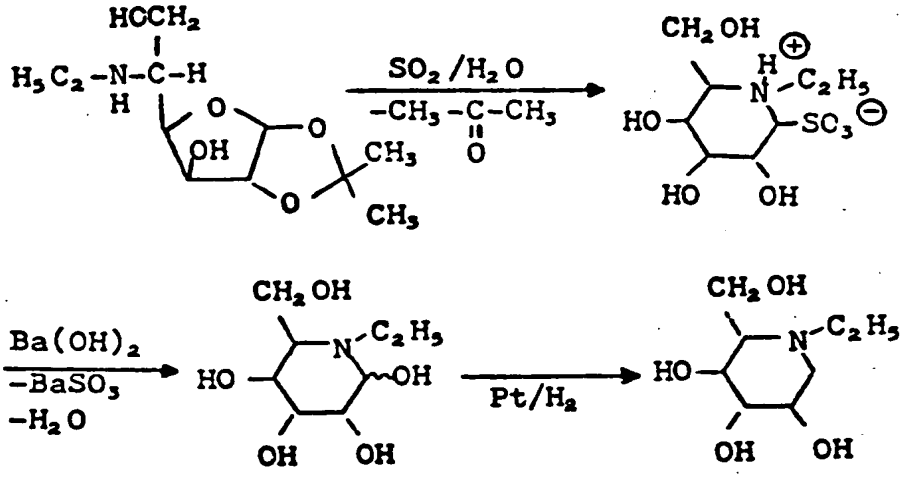
Z is an easily eliminated group, such as, for example, halide or $^{\ominus}O\text{-}SO_3H$, which is customary in alkylating agents.

In addition, compounds of the formula I are obtained, for example, when, in compounds of the formula I in which R_3 = $-CH_2OH$, the $-CH_2OH$ group is selectively converted into a $-CH_2\text{-}O\text{-}SO_2$-  group in a manner which is in itself known and this is either converted into the $-CH_3$ group by reduction or into an amino group by reduction, via a $-CH_2\text{-}N_3$ group. Compounds of the formula I are also obtained when, in compounds of the formula I in which R_3 = $-CH_2NH_2$, derivatives of the amino group of carboxylic acid chlorides or sulphonic acid chlorides, chlorocarbonic acid esters, isocyanates and isothiocyanates are prepared with alkyl halides, aldehydes or ketones in the presence of a hydrogen donor in a manner which is in itself known.

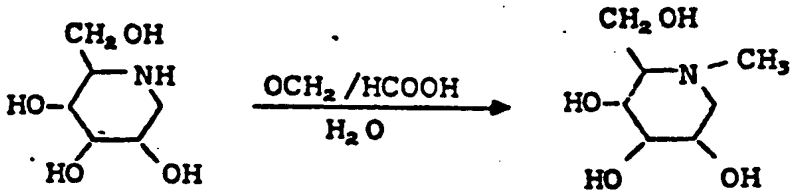
Compounds of the formula I in which R_1 is an aliphatic or aromatic radical which is substituted by an acylamino, sulphonylamino, alkoxycarbonylamino, ureido or thioureido group are obtained starting from compounds of the formula I in which R_1 is an aliphatic or aromatic radical which is substituted by an amino group, by reacting this amino group with carboxylic acid chlorides or sulphonic acid chlorides or with chlorocarbonic acid esters, isocyanates or isothiocyanates in a manner which is in itself known.

The individual procedures for the preparation of the active compounds according to the invention are illustrated below:

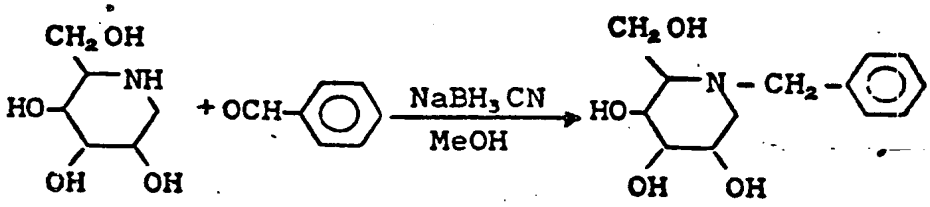
If a compound of the formula II in which R_1 = ethyl is used as the starting material, the course of the reaction can be represented as follows:



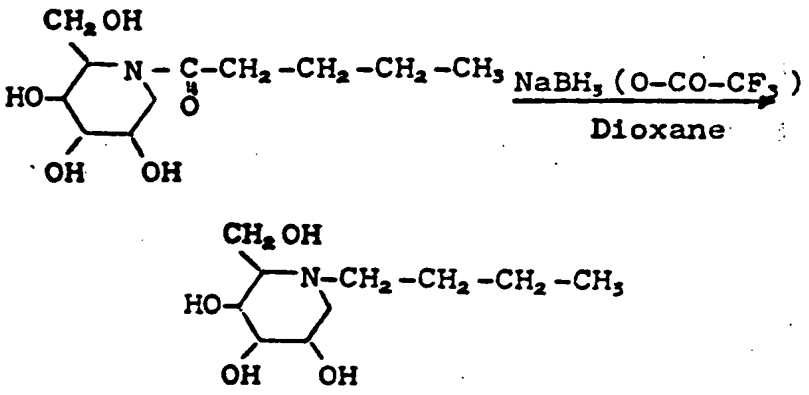
If 1-desoxynojirimycin of the formula V and formaldehyde are used as starting materials, the following equation results:



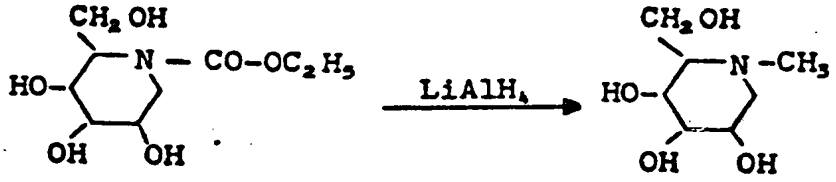
If benzaldehyde is used as the carbonyl compoennt, the reductive alkylation is carried out as follows:



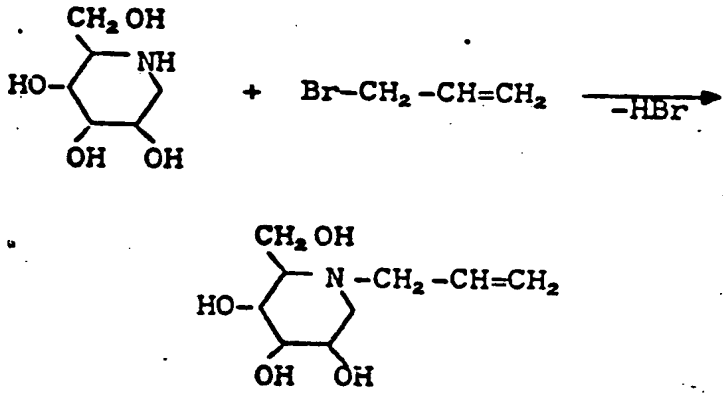
If acid amides of the formula VII are used as starting materials, the reaction can be described as follows:



Urethanes of the formula VIII, optionally in the form of derivatives provided with hydroxyl-protective groups, can be reduced to N-methyl-1-desoxynojirimycin with $LiAlH_4$:

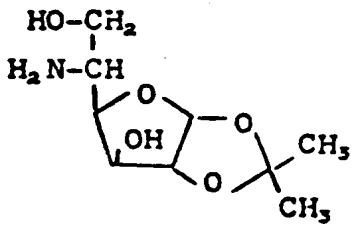


For the reaction of 1-desoxynojirimycin with alkylating agents, the reaction with allyl bromide may be indicated as an example:



Some of the compounds of the formula II used as starting materials are known. This is the case when R_3 is H, $-CH_2OH$ or $-CH_2NH_2$ and R_1 is H. Other compounds of the formula II or IIa are new; however, they can be prepared from compounds which are known from the literature by processes which are in themselves known.

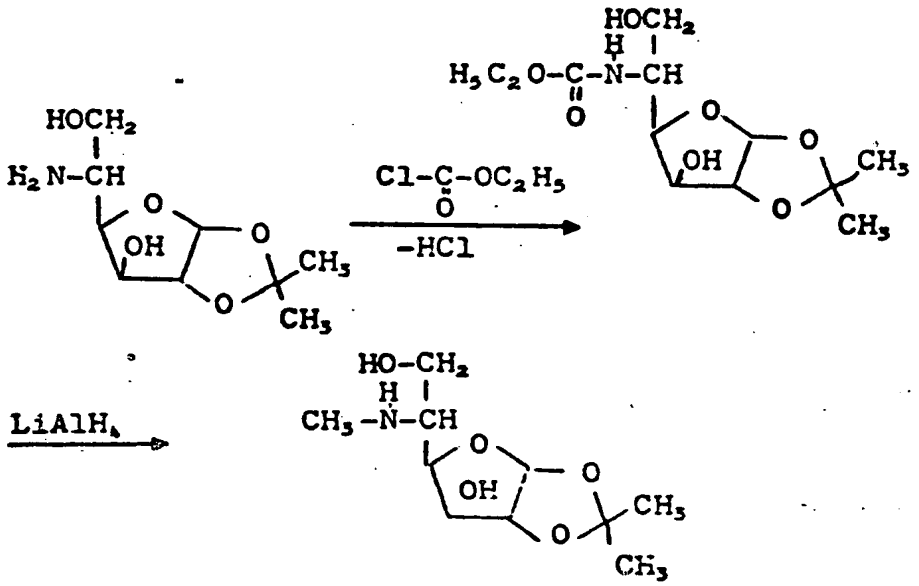
Thus, for example, it is possible to use the compound of the formula X, which is known from the literature,



X

as a starting material and to react this with carbonyl compounds of the formula VI in the presence of a hydrogen donor reducing agent to give compounds of the formula II.

Furthermore, it is possible to react the compound X with reactive acid derivatives to give acid amides or urethanes and to reduce these to amines with an amide-reducing agent. This may be illustrated by an example:

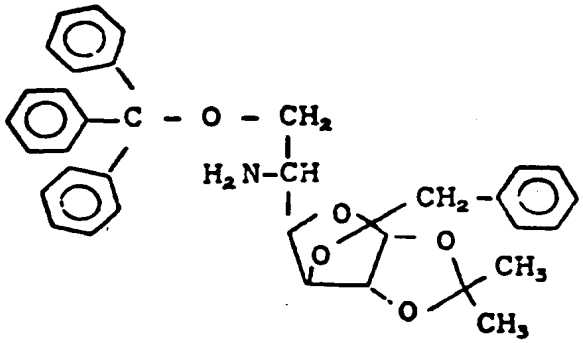


The compound of the formula X can also be reacted with reactive alkylating agents of the formula IX

$$Z - R_1 \qquad \text{IX}$$

to give compounds of the formula II.

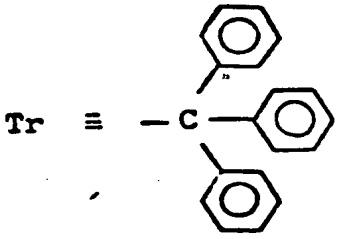
Furthermore, in the abovementioned reactions, instead of the compound X it is also possible to employ known partially protected derivatives of the formula XI.

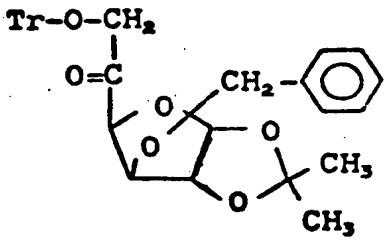


XI

and then to remove the trityl and benzyl protective groups in a known way, for example with sodium in liquid ammonia.

To prepare compounds of the formula II, it is also possible to react the compound of the formula XII, which is likewise known from the literature,





XII

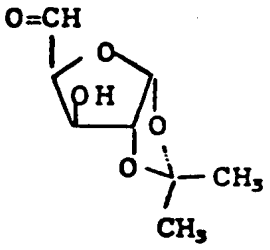
with amines of the formula XIII

$$R_1 - NH_2 \qquad \text{XIII}$$

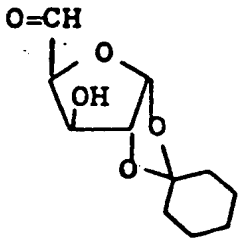
in the presence of a hydrogen donor reducing agent, for example in the presence of $NaBH_3CN$. As a rule, a diastereomer mixture is formed in this reaction. The diastereomer which is

not desired is appropr tely separated off at this stage or at a later stage by the customary chromatographic methods or by fractional crystallisation. Finally, the trityl and benzyl protective group are split off in a known way, for example with sodium in liquid ammonia.

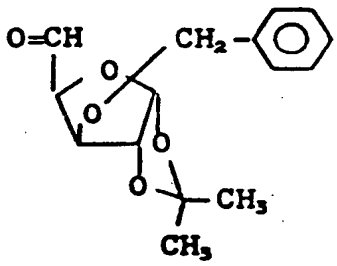
Moreover, new compounds of the formula II or IIa can also be obtained by reacting the degradation products of D-glucose, which are known from the literature, of the formulae XIV to XVI



XIV

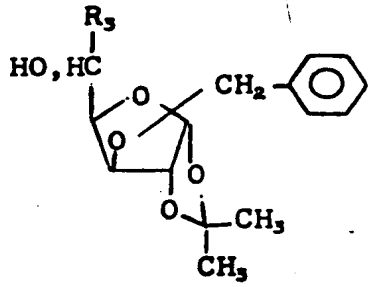


XV



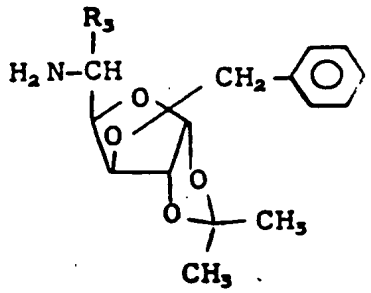
XVI

with reagents having a carbanion character, such as, for example, alkyl-Li or Grignard compounds or the Li salt of 1,3-dithiane, and converting the resulting compounds of the formula XVII



XVII

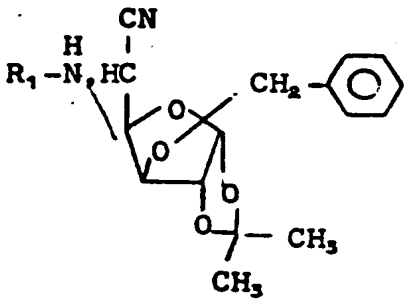
into the amine in a manner which is in itself known [S.INOUYE et al., Tetrahedron 23, 2125-2144] via the ketone and the oxime, whereupon, as a rule, a mixture of the gluco compound and ido compound forms, from which the desired gluco compound XVIII can be isolated by the customary chromatographic methods.



XVIII

Removal of the benzyl protective group by catalytic hydrogenation or with Na in liquid NH_3 then gives the compounds of the formula II.

Compounds of the formula XIX are obtained when the aldehydes of the formulae XIV to XVI are reacted with amines and hydrocyanic acid in a manner which is in itself known to give aminonitriles, for example XVI is reacted to give XIX

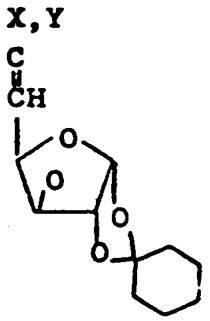


XIX

and in this case also, as a rule, the desired gluco compound must be separated off from the ido compound by customary

chromatographic methods. Further conversion of the nitrile group by hydrogenation or hydrolysis before or after the removal of the benzyl protective group leads to further compounds of the formula II.

The reaction of XIV to XVI with CH-acid compounds, such as, for example, nitroalkanes, alkylnitriles, CH-acid esters or ketones can also lead to compounds of the formula II. In this case, unsaturated compounds, for example of the formula XX, are obtained.



X = $-NO_2$, -CN or -COOalkyl

Y = H, alkyl or aryl

XX

either direct or by dehydrating the aldol addition products, and these compounds give compounds of the formula IIa by a Michael addition reaction with amines, after chromatographic separation of gluco and ido isomers.

The isopropylidene protective group is split off from the compounds of the formula II in a moderately strongly acid to weakly acid solution, preferably in a pH range between 1 and 4, in aqueous solution or in a water-miscible, water-containing organic solvent. Acids which can be used are dilute mineral acids, such as, for example, sulphuric acid, or also organic acids, such as acetic acid. The reaction is preferably carried out under atmospheric pressure and at a temperature between room temperature and the boiling point of the solvent.

In order to work up the reaction mixture, the acid is neutralised and separated off as a salt or with the aid of a

basic ion exchanger. The isolation of the compounds of the formula I in which R_2 = OH is then appropriately effected by careful removal of the solvent, for example by lyophilisation.

A preferred embodiment of the splitting off of the isopropylidene protective group from compounds of the formula II consists in saturating the aqueous or water-containing alcoholic solution of the compounds of the formula II with SO_2 and storing the saturated solution at temperatures between 20° and 50°C for several days. The compounds of the formula I are then obtained as bisulphite adducts (R_2 = $-SO_3H$), which in most cases readily crystallise, from which the compounds of the formula I can be liberated with the aid of, for example, aqueous $Ba(OH)_2$.

The compounds of the formula I in which R_2 = OH are reduced to compounds of the formula I in which R_2 = H by using alkali metal borohydrides, alkali metal cyanoborohydrides or dialkylaminoboranes. It is preferable to use sodium borohydride in aqueous solution or in a water-miscible water-containing organic solvent, such as, for example, dioxane, at room temperature or optionally elevated temperature. However, the reduction is very particularly preferably carried out catalytically with Pt or Pd as the catalyst or in the presence of Raney Ni. In this procedure, it is preferably carried out in an aqueous solution at room temperature.

The starting material of the formula V, in which R_3 = $-CH_2OH$, is known and is obtained either by catalytic hydrogenation of nojirimycin, which is obtainable by fermentation [S.INOUYE et al., Tetrahedron 23, 2125-2144 (1968)], or by extraction from mulberry tree bark (see DT-OS (German Published Specification) 2,656,602), or completely synthetically. 1-Desoxynojirimycin can also be prepared by a new advantageous

process by cultivating organisms of the Bacillaceae family in customary fermentation vessels in customary nutrient solutions at temperatures from about 15 to about 80°C for about 1 to about 8 days, with aeration, centrifuging off the cells and isolating the desoxy compound from the culture broth or the cell extracts by customary purification processes [German Patent Application P 26 58 563.7 - (Le A 17 587)].

The carbonyl compounds of the formula VI are either known or can be prepared by standard processes.

In detail, typical examples which may be mentioned are: straight-chain or branched alkylaldehydes, such as formaldehyde, acetaldehyde, n-propanal, n-butanal, 2-methylpropanal, n-pentanal, 2-methylbutanal, 3-methylbutanal, 2,2-dimethylpropanal, n-hexanal, 2-ethylbutanal, n-heptanal and n-octanal; alkenylaldehydes, such as propenal, 2-methylpropenal, 2-butenal, 2-methyl-2-butenal and 2-ethyl-2-hexenal; cyclic aldehydes, such as cyclopropanecarbaldehyde, cyclopentanecarbaldehyde, cyclopentanecetaldehyde and cyclohexanecarbaldehyde; benzaldehyde, o-, m- and p-toluenecarbaldehyde and phenylacetaldehyde; straight-chain and branched alkylaldehydes which are substituted by hydroxyl, such as 5-hydroxypentanal, 2-hydroxy-3-methylbutanal, 2-hydroxy-2-methylpropanal, 4-hydroxybutanal, 2-hydroxypropanal and 8-hydroxyoctanal; straight-chain and branched alkylaldehydes which are substituted by amino, such as 5-aminopentanal, 2-aminopropanal, 3-aminopropanal, 4-aminobutanal, 2-amino-3-methylbutanal, 8-aminooctanal and mono-N-alkyl derivatives thereof; and straight-chain and branched alkylaldehydes which are disubstituted by amino and hydroxyl, such as 2-hydroxy-5-aminopentanal, 3-hydroxy-3-methyl-4-aminobutanal, 2-hydroxy-4-aminobutanal, 2-hydroxy-3-aminopropanal, 2-hydroxy-2-methyl-3-aminopropanal,

2-amino-3-hydroxyoctanal and mono-N-alkyl derivatives thereof.

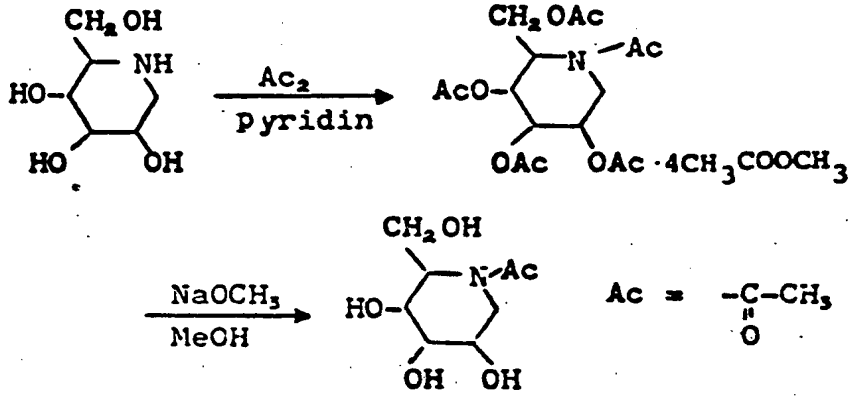
Furthermore: methoxy-acetaldehyde, ethoxy-acetaldehyde, n-propoxy-acetaldehyde, i-propoxy-acetaldehyde, n-butoxy-acetaldehyde, i-butoxy-acetaldehyde, tert.-butoxy-acetaldehyde, cyclopropylmethoxy-acetaldehyde, cyclopropoxy-acetaldehyde, 2-methoxy-ethoxy-acetaldehyde, 2-ethoxy-ethoxy-acetaldehyde, 2-methoxy(1-methyl-ethoxy)-acetaldehyde, 2-ethoxy(1-methyl-ethoxy)-acetaldehyde, phenoxy-acetaldehyde, 2-methoxy-2-methyl-acetaldehyde, 2-ethoxy-2-methyl-acetaldehyde, 2-n-propoxy-2-methyl-acetaldehyde, 2-(i-propoxy-)2-methyl-acetaldehyde, 2-(n-butoxy)-2-methyl-acetaldehyde, 2-(i-butoxy)-2-methyl-acetaldehyde, 2-(tert.-butoxy)-2-methyl-acetaldehyde, 2-cyclopropylmethoxy-2-methyl-acetaldehyde, 2-cyclopropoxy-2-methyl-acetaldehyde, 2-methoxy-ethoxy-α-methyl-acetaldehyde, 2-ethoxy-ethoxy-α-methyl-acetaldehyde, 2-methoxy-(1-methyl-ethoxy)α-methyl-acetaldehyde, 2-methoxy-2,2-dimethyl-acetaldehyde, 2-ethoxy-2,2-dimethyl-acetaldehyde, 2-cyclopropylmethoxy-acetaldehyde, 2-ω-butoxy-2,2-dimethyl-acetaldehyde, methylthio-acetaldehyde, ethylthio-acetaldehyde, n-propylthio-acetaldehyde, i-propylthio-acetaldehyde, cyclopropyl-methylthio-acetaldehyde, 3-methoxy-propanal, 3-ethoxy-propanal, 3-n- and 3-i-propoxy-propanal, 3-n-, 3-i- and 3-tert.-butoxy-propanal, 3-cyclopropoxy-propanal, 3-cyclopropylmethoxy-propanal, 3-methoxy-3-methyl-propanal, 3-ethoxy-3-methyl-propanal, 3-n- and 3-i-propoxy-3-methyl-propanal, 3-n-, 3-i- and 3-tert.-butoxy-3-methyl-propanal, 2,3 and 4-methoxy-butanal, 2,3 and 4-ethoxy-butanal, 2-methylthio-propanal, 2-ethylthio-propanal, 3-methylthio-propanal, 3-ethylthio-propanal, 2-methylthio-butanal, 3-methylthio-butanal, 4-methylthio-butanal, furfurol, tetrahydrofurfurol, thiophene, 5-bromothiophene, 5-methylfurfurol and pyrane-carbaldehyde.

borane), a protic solvent is usually used. A suitable protic solvent is, in particular, a lower alkanol. However, water or an aqueous lower alkanol (for example aqueous methanol or ethanol) or other aqueous solvent systems, such as, for example, aqueous dimethylformamide, aqueous hexamethylphosphoric acid triamide, aqueous tetrahydrofurane or aqueous ethylene glycol dimethyl ether, can also be used.

The process is usually carried out in a pH range from 1 to 11, and a pH range between 4 and 7 is preferred.

The acid amides of the formula VII and urethanes of the formula VIII are known in some cases, or they can be obtained by known processes from the compound V and reactive acid derivatives, which can also be formed in situ from the free acids.

In this procedure, the reaction can be carried out in a manner such that only the amino group of the compound V reacts with the acid derivative, for example by using excess acid anhydride in an aqueous or alcoholic solution, or such that the peracylated compounds first form and are then converted into the N-acylated compounds by reaction with alcoholic ammonia or by trans-esterification catalysed by alkali metal alcoholate. The latter process may be illustrated by an example:

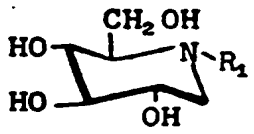


The acid amides of the formula II can be reduced to amines of the formula I (R = H) with complex metal hydrides or also with boron hydride compounds. It is preferable to use $NaBH_4$ in pyridine or also sodium acyloxyborohydrides, particularly sodium trifluoroacetoxyborohydride. As a rule, the reducing agents are employed in excess. Sodium trifluoroacetoxyborohydride is produced in situ from sodium borohydride and trifluoroacetic acid. Possible solvents are, in addition to pyridine, polar aprotic solvents, such as dioxane, tetrahydrofurane or diglyme. The reaction is preferably carried out at the boiling point of the solvent. $LiAlH_4$ can also optionally be used for the reduction, preferably when the hydroxyl groups are first protected in the customary way.

The reactive alkylating agents of the formula IX are known or can be prepared by customary processes. The reaction with the compound V is carried out in inert organic solvents at room temperature up to the boiling point, with or without the addition of an acid-binding agent.

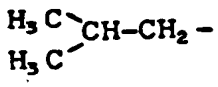
In detail, new active compounds which may be mentioned are:

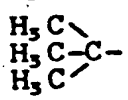
Compounds of the formula



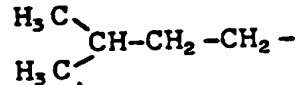
R_1
CH_3
CH_3CH_2-
$CH_3CH_2CH_2-$
$CH_3\underset{\displaystyle CH_3}{C}HCH_3$
$CH_3CH_2CH_2CH_2-$
$CH_3-\underset{\displaystyle CH_3}{C}H-CH_2-CH_3$

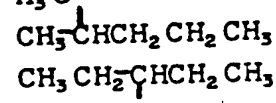
R_1





$CH_3(CH_2)_3-CH_2-$

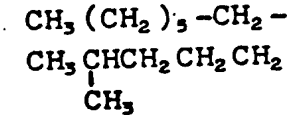


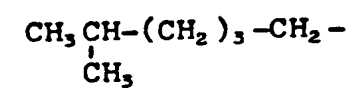


$CH_3CH(CH_3)CH_2CH_2-$

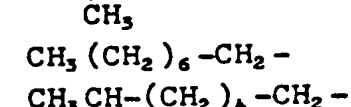
$CH_3(CH_2)_4-CH_2-$

$CH_3(CH_2)_5-CH_2-$





$CH_3(CH_2)_6-CH_2-$



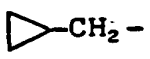
$CH_3-(CH_2)_8-CH_2-$

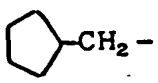
$CH_3-(CH_2)_{10}-CH_2-$

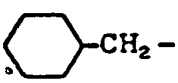
$CH_3-(CH_2)_{12}-CH_2-$

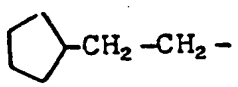
$CH_3-(CH_2)_{14}-CH_2-$

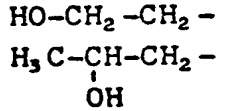
$CH_3-(CH_2)_{16}-CH_2-$











R_1

$HOH_2C-CH_2-CH_2-$

$HOH_2C-CH_2-CH_2-CH_2-$

$HOH_2C-(CH_2)_3-CH_2-$

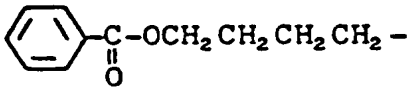
$CH_3-\underset{\displaystyle CH_3}{\underset{|}{CH}}-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-$

$HO-CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-CH_2-$

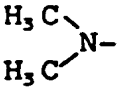
$CH_3OCH_2-CH_2-$

$C_3H_7OCH_2-CH_2-$

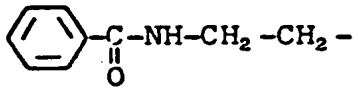
$CH_3COOCH_2-CH_2-$



$H_2N-CH_2-CH_2-$



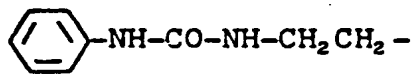
$CH_3CONH-CH_2-CH_2-$



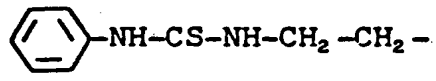
$C_2H_5OC(=O)NH-CH_2-CH_2-$

$CH_3CO-\underset{\displaystyle CH_3}{\underset{|}{N}}-CH_2-CH_2-$

$CH_3NH-CO-NH-CH_2CH_2-$



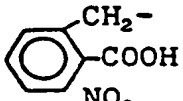
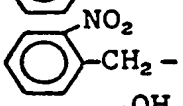
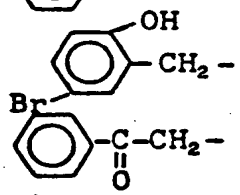
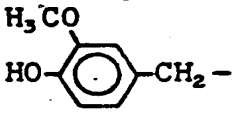
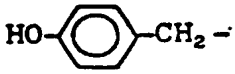
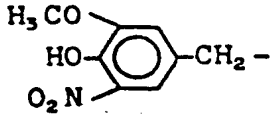
$CH_3NH-CS-NH-CH_2CH_2-$



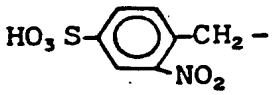
$H_2N-CH_2CH_2CH_2-$

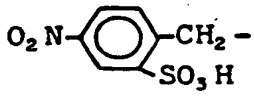
$CH_3CONHCH_2CH_2CH_2-$

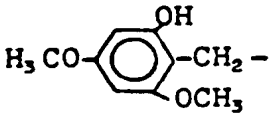
$CH_3NHCONHCH_2CH_2CH_2-$

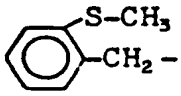
	R_1
	$H_2N-CH_2CH_2CH_2CH_2-$
	$H_2C=CH-CH_2-$
	$H_3C-HC=CH-CH_2-$
	$H_2C=CH-CH_2-CH_2-$
	$H_2C=CH-CH_2-CH_2-CH_2-CH_2-$
	$H_2C=CH-(CH_2)_7-CH_2-$
	$HOOC-CH_2-$
	$HOOC-CH_2-CH_2-$
	$H_5C_2OOC-CH_2-CH_2-$
	$H_2N-\overset{\overset{O}{\|}}{C}-CH_2-$
	$C_2H_5HN-\overset{\overset{O}{\|}}{C}-CH_2$
	$C_4H_9-HN-\overset{\overset{O}{\|}}{C}-CH_2$
	$HO_3S-CH_2CH_2CH_2-$
	$H_2NO_2S-CH_2CH_2CH_2-$
	
	
	
	
	$H-C\equiv C-CH_2-$
	
	

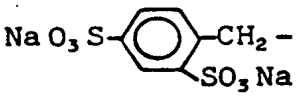
R_1

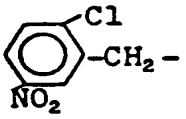


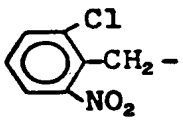


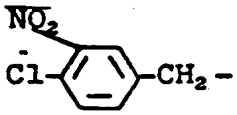


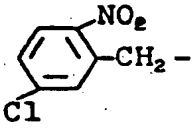


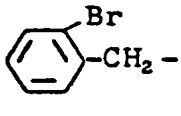


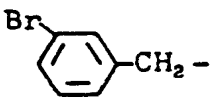












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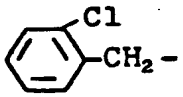
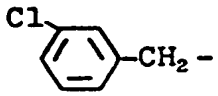
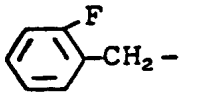
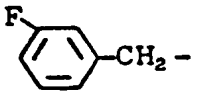
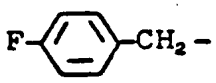
R_1

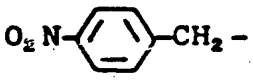


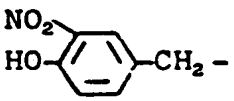


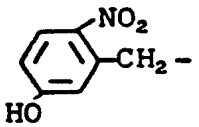


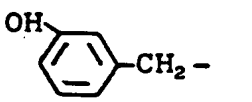


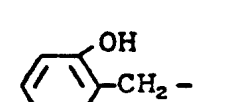




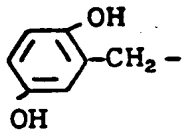


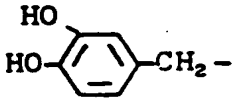


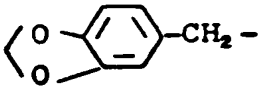


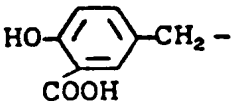


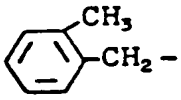
R_1

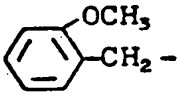


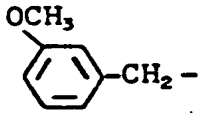


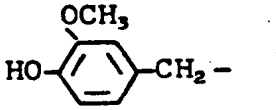


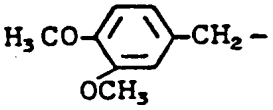


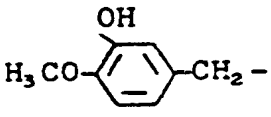


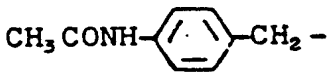




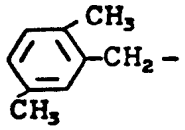


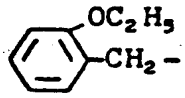


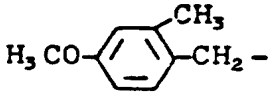


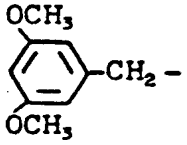


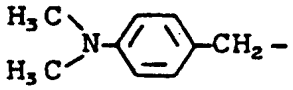
R_1

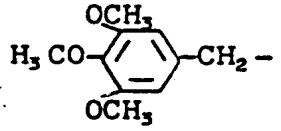


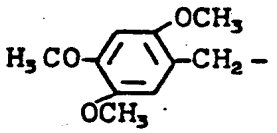


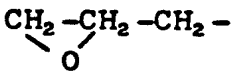


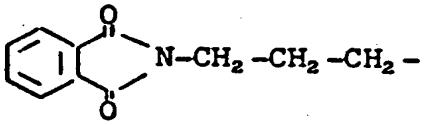


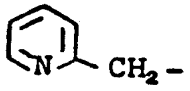












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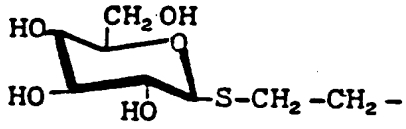
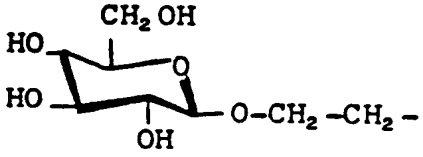
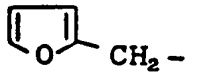
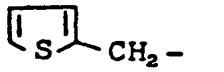
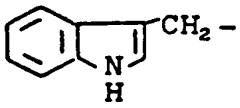
R_1

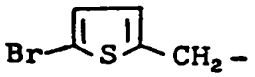


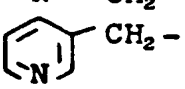


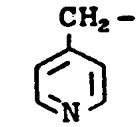


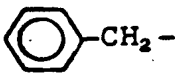


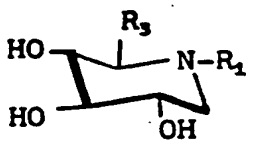


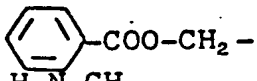
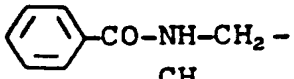
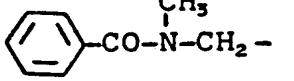
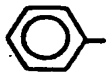
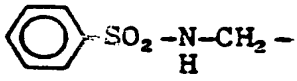


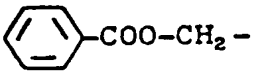
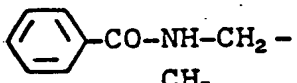
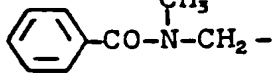
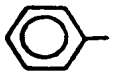
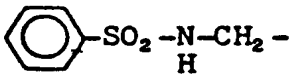


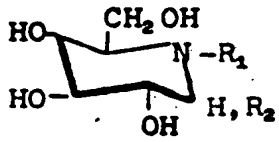




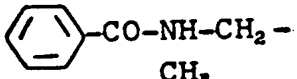
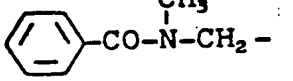
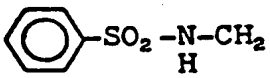
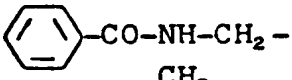
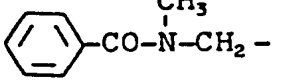
Compounds of the formula 

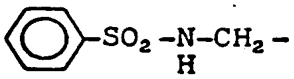
R_1	R_3
H–	CH_3–
H–	CH_3CH_2–
H–	$CH_3CH_2CH_2$–
H–	$CH(CH_2)_6$–CH_2–
H–	H_3C–O–CH_2–
H–	H_5C_2–O–CH_2–
H–	H_3C–COO–CH_2–
H–	
H–	H_2N–CH_2–
H–	CH_3CO–NH–CH_2–
H–	
H–	
H–	$CH_3NHCONH$–CH_2–
H–	
H–	CH_3–CH_2–N(H)–C(=S)–NH–CH_2–
H–	C_2H_5OCONH–CH_2–
H–	HO–CH_2–CH_2–
H–	
H–	–COOH
H–	$-CONH_2$
H–	H_3C–SO_2–N(H)–CH_2–
H–	H_3C–H_2C–SO_2–N(H)–CH_2–
H–	

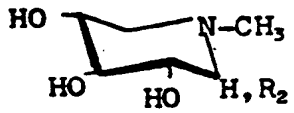
R_1	R_3
CH_3-	CH_3-
CH_3-	CH_3CH_2-
CH_3-	$CH_3CH_2CH_2-$
CH_3-	$CH_3(CH_2)_6-CH_2-$
CH_3-	$H_3C-O-CH_2-$
CH_3-	$H_5C_2-O-CH_2-$
CH_3-	$H_3C-COO-CH_2-$
CH_3-	
CH_3-	H_2N-CH_2-
CH_3-	$CH_3CO-NH-CH_2-$
CH_3-	
CH_3-	
CH_3-	$CH_3NHCONH-CH_2-$
CH_3-	
CH_3-	$CH_3-CH_2-N(H)-C(=S)-NH-CH_2-$
CH_3-	$C_2H_5OCONH-CH_2-$
CH_3-	$HO-CH_2-CH_2-$
CH_3-	
CH_3-	$-COOH$
CH_3-	$-CONH_2$
CH_3-	$H_3C-SO_2-N(H)-CH_2-$
CH_3-	$H_3C-H_2C-H_2C-SO_2-N(H)-CH_2-$
CH_3-	

Compounds of the formula 

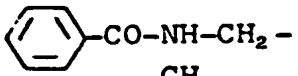
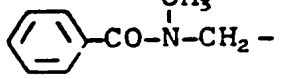
With respect to the configuration at the C-2 atom, the examples listed below include both the α-form and the β-form

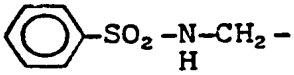
R_1	R_2
H–	H_2N-CH_2-
H–	$CH_3CO-NH-CH_2-$
H–	
H–	
H–	$CH_3NHCONH-CH_2-$
H–	
H–	$CH_3-CH_2-N(H)-C(=S)-NH-CH_2-$
H–	$C_2H_5OCONH-CH_2-$
H–	$-COOH$
H–	$-COOC_2H_5-$
H–	$-CONH_2$
H–	$H_3C-SO_2-N(H)-CH_2$
H	$H_3C-H_2C-H_2C-SO_2-N(H)-CH_2-$
H–	
H–	$HO-CH_2-$
H–	$H_5C_2-COO-CH_2-$
CH_3-	H_2N-CH_2-
CH_3-	$CH_3CO-NHCH_2-$
CH_3-	
CH_3-	
CH_3-	$CH_3NHCONH-CH_2-$

R_1	R_2
CH_3-	
CH_3-	$CH_3-CH_2-N(H)-C(=S)-NH-CH_2-$
CH_3-	$C_2H_5OCONH-CH_2-$
CH_3-	$-COOH$
CH_3-	$-COOC_2H_5$
CH_3-	$-CONH_2$
CH_3-	$H_3C-SO_2-N(H)-CH_2-$
CH_3-	$H_3C-H_2C-H_2C-SO_2-N(H)-CH_2-$
CH_3-	
CH_3-	$HO-CH_2-$
CH_3-	$H_5C_2-COO-CH_2-$
CH_3-	$-OH$
CH_3-	$-SO_3H$
CH_3-	$-CN$
CH_3-	$-OCH_3$
CH_3-	$-O-CH_2-CH_2-CH_2-CH_3$
CH_3-	$-SH$
CH_3-	$-S-CH_2-CH_3$
CH_3-	$-NH_2$
CH_3-	$-NH-CH_3$

Compounds of the formula 

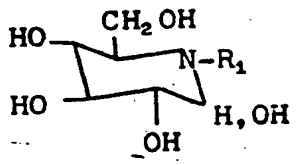
With respect to the configuration at the C-2 atom, the examples listed below include both the α-form and the β-form

R_2
H_2N-CH_2-
$CH_3CO-NH-CH_2-$


$CH_3NHCONH-CH_2-$

$CH_3-CH_2-N(H)-C(=S)-NH-CH_2-$
$C_2H_5OCONH-CH_2-$
$-COOH$
$-COOC_2H_5$
$-CONH_2$
$H_3C-SO_2-N(H)-CH_2-$
$H_3C-H_2C-H_2C-SO_2-N(H)-CH_2-$

$HO-CH_2-$
$H_5C_2-C(=O)-O-CH_2-$

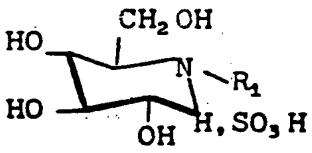
R_2	R_2
$-OH$	$-O-CH_2-CH_2-CH_2-CH_3$
$-CN$	$-SH$
$-SO_3H$	$-S-CH_2-CH_3$
$-OCH_3$	$-NH_2$
	$-NH-CH_3$

Compounds of the formula

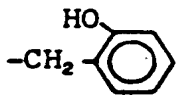


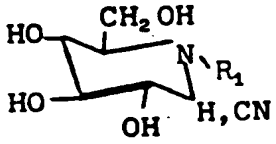
R_1
$-CH_2-CH_3$
$-CH_2-CH_2-CH_2-CH_3-$
$-CH_2-(CH_2)_{16})-CH_3-$
$-CH(CH_3)(CH_3)$
$-CH_2-C_6H_5$
$-CH_2-CH=CH_2-$
$-CH_2-CH_2-OCH_3-$
$-CH_2-CH_2-N(CH_3)(CH_3)$
$-CH_2-C_6H_4-OH$

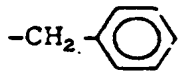
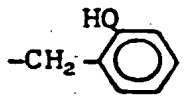
Compounds of the formula



R_1
$-CH_2-CH_3$
$-CH_2-CH_2-CH_2-CH_3$
$-CH_2-(CH_2)_{16}-CH_3$
$-CH(CH_3)(CH_3)$
$-CH_2-C_6H_5$
$-CH_2-CH=CH_2$
$-CH_2-CH_2-OCH_3$

R_1
$-CH_2-CH_2-N(CH_3)_2$


Compounds of the formula 

R_1
$-CH_2-CH_3$
$-CH_2-CH_2-CH_2-CH_3$
$-CH_2-(CH_2)_{16}-CH_3$
$-CH(CH_3)_2$

$-CH_2-CH=CH_2$
$-CH_2-CH_2-OCH_3$
$-CH_2-CH_2-N(CH_3)_2$


The inhibitors according to the invention are suitable for use as therapeutic agents for the following indications: pre-diabetes, gastritis, constipation, caries, atherosclerosis and, in particular, adiposity, diabetes and hyperlipoprotaemia.

In order to broaden the spectrum of activity, it can be advisable to combine inhibitors for glycoside-hydrolases which

complement one another in their action, the combinations being either combinations of the inhibitors according to the invention with one another or combinations of the inhibitors according to the invention with inhibitors which are already known. Thus, for example, it can be appropriate to combine saccharase inhibitors according to the invention with amylase inhibitors which are already known.

In some cases, combinations of the inhibitors according to the invention with known oral antidiabetic agents (β-cytotropic sulphonylurea derivatives and/or biguanides having an action on the blood sugar) and with blood lipid-lowering active compounds, such as, for example, clofibrate, nicotinic acid, cholestyramine and others.

The compounds can be administered without dilution, for example as a powder or in a gelatine casing, or in combination with an excipient in a pharmaceutical composition.

Pharmaceutical formulations can contain a relatively large or relatively small amount of the inhibitor, for example 0.1% to 99.5%, combined with a pharmaceutically acceptable non-toxic, inert excipient, it being possible for the excipient to contain one or more solid, semi-solid or liquid diluents, fillers and/or non-toxic, inert and pharmaceutically acceptable formulation auxiliary. Such pharmaceutical formulations are preferably in the form of dosage units, that is to say physically discrete units containing a particular amount of the inhibitor and corresponding to a fraction or a multiple of the dose which is required for causing the desired inhibiting action. The dosage units can contain 1, 2, 3, 4 or more individual doses or a ½, 1/3 or 1/4 of an individual dose. An individual dose preferably contains an amount of active compound which is sufficient to achieve the desired inhibiting

action on administration according to a previously determined dosage plan of one or more dosage units, a whole, a half or a third or a quarter of the daily dose usually being administered at all the main and secondary mealtimes of the day. Other therapeutic agents can also be taken. Although the dosage and the dosage plan should be carefully considered in each case, applying thorough expert judgement and taking into account the age, the weight and the condition of the patient and the nature and the severity of the disease, the dosage is usually in a range between about 1 to about 1×10^4 SIU/kg of body weight per day. In some cases a sufficient therapeutic action is achieved with a relatively low dose, whilst in other cases a relatively large dose will be required.

Oral administration can be carried out using solid and liquid dosage units, such as, for example, powders, tablets, dragées, capsules, granules, suspensions, solutions and the like.

Powders are prepared by comminuting the substance to a suitable size and mixing it with a pharmaceutical excipient, which has also been comminuted. Although an edible carbohydrate, such as, for example, starch, lactose, sucrose or glucose, is usually used for this purpose and can also be used here, it is desirable to employ a carbohydrate which cannot be metabolised, such as, for example, a cellulose derivative.

Sweeteners, flavouring additives, preservatives, dispersing agents and dyestuffs can also be co-used.

Capsules can be prepared by formulating the powder mixture described above and filling gelatine casings which have already been formed. Lubricants, such as, for example, silica gel, talc, magnesium stearate, calcium stearate or solid polyethylene glycol, can be added to the powder mixture before

the filling operation. A disintegrating agent or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, can also be added to the mixture in order to improve the accessibility of the inhibitor when the capsule is taken.

Tablets are manufactured, for example, by preparing a powder mixture, coarse or fine-grained, and adding a lubricant and disintegrating agent. Tablets are formed from this mixture. A powder mixture is prepared by mixing the substance, which has been comminuted in a suitable manner, and a diluent or another excipient as described above is added. A binder is optionally added: for example carboxymethylcellulose, alginates, gelatine or polyvinylpyrrolidones, and a solution retarder, such as, for example, paraffin, a resorption accelerator, such as, for example, a quaternary salt and/or an adsorbent, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated together with a binder, such as, for example, syrup, starch paste or gum acacia, or solutions of cellulose or polymeric materials. Thereafter, the product is pressed through a coarse sieve. Alternatively, it is possible to allow the powder mixture to run through a tablet machine and to comminute the resulting non-uniformly shaped pieces down to the particle size. So that the particles do not jam in the tablet-forming nozzles, a lubricant can be added, such as, for example, stearic acid, a stearate salt, talc or mineral oil. This mixture which has been lubricated is then pressed into tablet form. The active compounds can also be combined with free-flowing inert excipients and brought directly into tablet form, omitting the granulation or comminution steps. The product can be provided with a clear or opaque protective casing, for example a

coating of shellac, a coating of sugar or polymeric substances and a polished casing of wax. Dyestuffs can be added to these coatings so that a distinction can be made between the different dosage units.

The formulation forms to be administered orally, such as, for example, solutions, a syrup and elixirs, can be prepared in dosage units so that a particular amount of formulation contains a particular amount of active compound. The syrup can be prepared by dissolving the active compound in an aqueous solution which contains suitable flavouring substances; elixirs are obtained using non-toxic, alcoholic excipients. Suspensions can be prepared by dispersing the compound in a non-toxic excipient. Solubilisers and emulsifying agents, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol esters, preservatives, and additives which improve the flavour, such as, for example, peppermint oil or saccharin and the like, can also be added.

Dosage instructions can be given on the capsule. Moreover, the dosage can be made safe so that the active compound is released in a delayed manner, for example by holding the active compound in polymeric substances, waxes or the like.

In addition to the abovementioned pharmaceutical compositions, foodstuffs containing these active compounds can also be prepared; for example sugar, bread, potato products, fruit juice, beer, chocolate and other confectionery, and preserves, such as, for example, jam, a therapeutically active amount of at least one of the inhibitors according to the invention having been added to these products.

The food products produced using the active compounds according to the invention are suitable for use both in the diet of patients suffering from metabolism disorders and for

the nutrition of healthy persons in the sense of a method of nutrition for preventing metabolism disorders.

Furthermore, the inhibitors according to the invention have the property, in animals, of influencing to a high degree the ratio of the proportion of undesired fat to the proportion of desired meat of low fat content (lean meat) in favour of the lean meat. This is of particular importance for the rearing and keeping of agricultural stock animals, for example in the fattening of pigs, but is also of considerable importance for the rearing and keeping of other stock animals and pets. Furthermore, the use of the inhibitors can lead to a considerable rationalisation of the feeding of the animals, both in respect of time, quantity and quality. Since they cause a certain delay in digestion, the residence time of the nutrients in the digestive tract is extended, whereby ad libitum feeding associated with less expense is made possible. Furthermore, in many cases there is a considerable saving of valuable protein feed when the inhibitors according to the invention are used.

The active compounds can thus be used in virtually all sections of animal nutrition as agents for reducing the formation of fatty layers and for the saving of feed protein.

The activity of the active compounds here is essentially independent of the nature and the sex of the animals. The active compounds prove particularly valuable in species of animals which tend generally to deposit relatively large amounts of fat, or tend to do so during certain stages of their life.

The following stock animals and pets may be mentioned as examples of animals for which the inhibitors for reducing the formation of fatty layers and/or for saving feed protein

can be employed: warm-blooded animals, such as cattle, pigs, horses, sheep, goats, cats, dogs, rabbits, fur-bearing animals, for example mink and chinchillas, and other pets, for example guineapigs and hamsters, laboratory animals and zoo animals, for example rats, mice, monkeys and the like, poultry, for example broilers, chickens, geese, ducks, turkeys and pigeons, parrots and canaries, and cold-blooded animals, such as fish, for example carp, and reptiles, for example snakes.

Because of the favourable properties of the active compounds, the amount of active compounds administered to the animals in order to achieve the desired effect can be substantially varied. It is preferably about 0.5 mg to 2.5 g in particular 10 to 100 mg/kg, of feed per day. The period over which the active compound is administered can be from a few hours or days to several years. The appropriate amount of active compound and the appropriate period over which it is administered are closely connected with the object of feeding. In particular, they depend on the nature, the age, the sex and the state of health and the method of keeping the animals and can be easily determined by any expert.

The active compounds according to the invention are administered to the animals by the customary methods. The nature of the administration depends, in particular, on the nature, the behaviour and the general condition of the animals. Thus it is possible to carry out the administration orally once or several times daily, at regular or irregular intervals. In most cases, oral administration, in particular in the rhythm of the food and/or drink intake of the animals, is to be preferred for reasons of expediency.

The active compounds can be administered as pure substances or in the formulated form, the formulated form being

understood both as a premix, that is to say mixed with non-toxic inert carriers of any desired nature, and also as part of a total ration in the form of a supplementary feed and as a constituent of the mixture of a mixed feed by itself. Administration of suitable formulations by means of the drinking water is also included.

The active compounds, optionally in the formulated form, can also be administered, in a suitable form, together with other nutrients and active compounds, for example mineral salts, trace elements, vitamins, proteins, energy carriers (for example starch, sugar or fats), dyestuffs and/or flavouring substances or other feedstuff additives, such as, for example, growth promoters. The active compounds can be administered to the animals before, during or after the food intake.

Oral administration together with the feed and/or drinking water is advisable, the active compounds being added to the total amount or only to parts of the feed and/or drinking water, depending on the requirement.

The active compounds can be added to the feed and/or the drinking water according to customary methods by simple mixing as the pure substances, preferably in the finely divided form, or in the formulated form mixed with edible, non-toxic carriers, and optionally also in the form of a premix or a feed concentrate.

The feed and/or drinking water can, for example, contain the active compounds according to the invention in a concentration of about 0.001 to 5.0%, in particular 0.02 to 2.0% (weight). The optimum level of the concentration of the active compound in the feed and/or drinking water depends, in particular, on the amount of feed and/or drinking water

intake of the animals and can be easily determined by any expert.

The nature of the feed and its composition is not important here. It is possible to use all the current, commercially available or special feed compositions, which preferably contain the customary balance of energy substances and proteins, including vitamins and mineral substances, necessary for balanced nutrition. The feed can be composed, for example, of vegetable substances, for example shredded oilcake, shredded cereal and cereal by-products, but also of hay, silage fodder, beets, and other forage plants, of animal substances, for example meat and fish products, bonemeal, fats and vitamins, for example A, D, E, K and B-complex, as well as special sources of protein, for example yeasts and certain aminoacids, and mineral substances and trace elements, such as, for example, phosphorus and iron, zinc, manganese, copper, cobalt, iodine and the like.

Premixes can preferably contain about 0.1 to 50%, in particular 0.5 to 5.0% (weight) of, for example, N-methyl-1-desoxynojirimycin, in addition to any desired edible carriers and/or mineral salts, for example carbonated feed lime, and are prepared by the customary mixing methods.

Mixed feeds preferably contain 0.001 to 5.0%, in particular 0.02 to 2.0% (weight), for example, of N-methyl-1-desoxynojirimycin, in addition to the customary raw material components of a mixed feed, for example shredded cereal or cereal by-products, shredded oilcake, animal protein, minerals, trace elements and vitamins. They can be prepared by the customary mixing methods.

The active compounds in premixes and mixed feedstuffs can preferably also be appropriately protected from air, light

and/or moisture by suitable agents which cover their surface, for example with non-toxic waxes or gelatine.

The following is an example of the composition of a finished mixed feed, for poultry, containing an active compound according to the invention: 200 g of wheat, 340 g of maize, 360.3 g of coarse soya bean meal, 60 g of beef tallow, 15 g of dicalcium phosphate, 10 g of calcium carbonate, 4 g of iodinated sodium chloride, 7.5 g of a vitamin/mineral mixture and 3.2 g of an active compound premix give, after careful mixing, 1 kg of feed.

The vitamin/mineral mixture consists of: 6,000 I.U. of vitamin A, 1,000 I.U. of vitamin D_3, 10 mg of vitamin E, 1 mg of vitamin K_3, 3 mg of riboflavin, 2 mg of pyridoxine, 20 mcg of vitamin B_{12}, 5 mg of calcium pantothenate, 30 mg of nicotinic acid, 200 mg of choline chloride, 200 mg of $MnSO_4 \times H_2O$, 140 mg of $ZnSO_4 \times 7H_2O$, 100 mg of $FeSO_4 \times 7H_2O$ and 20 mg of $CuSO_4 \times 5H_2O$. The active compound premix contains, for example, N-methyl-1-desoxynojirimycin in the desired amount, for example 1,600 mg, and in addition 1 g of DL-methionine and enough soya bean flour to form 3.2 g of premix.

The following is an example of the composition of a mixed feed, for pigs, which contains an active compound of the formula I: 630 g of shredded cereal feed (composed of 200 g of shredded maize, 150 g of shredded barley, 150 g of shredded oats and 130 g of shredded wheat), 80 g of fishmeal, 60 g of coarse soya bean meal, 58.8 g of tapioca flour, 38 g of brewer's yeast, 50 g of a vitamin/mineral mixture for pigs (composition, for example, as in the chicken feed), 30 g of linseed cake meal, 30 g of maize gluten feed, 10 g of soya bean oil, 10 g of cane sugar molasses and 2 g of active compound premix (composition, for example, in the chicken feed) give,

after careful mixing, 1 kg of feed.

The feed mixtures indicated are intended, preferably, for rearing and fattening chicken or pigs respectively; however, they can also be used in an identical or similar composition for rearing and fattening other animals.

The inhibitors can be used individually or also in any desired mixtures with one another.

In vitro saccharase inhibition test

The in vitro saccharase inhibition test makes it possible to determine the enzyme-inhibitory activity of a substance by comparison of the activity of the solubilised intestinal disaccharidase complex in the presence and in the absence (so-called 100% value) of the inhibitor. A virtually glucose-free sucrose (glucose <100 ppm) is used here as the substrate which determines the specificity of the inhibition test; the determination of enzyme activity is based on the spectrophotometric determination of glucose liberated, using glucose dehydrogenase and nicotinamide-adenine dinucleotide as the cofactor.

One saccharase inhibitor unit (SIU) is defined as that inhibitory activity which, in a defined test batch, reduces a given saccharolytic activity by one unit (saccharase unit = SU); the saccharase unit is defined here as that enzyme activity which splits off one µmol of sucrose per minute under given conditions and thus leads to the liberation of one µmol each of glucose, which is determined in the test, and fructose, which is not recorded in the test.

The intestinal disaccharidase complex is obtained from swine small intestine mucosa by tryptic digestion, precipitation from 66% strength ethanol at -20°C, taking up of the precipitate in 100 mM phosphate buffer, pH 7.0, and finally dialysis

against the same buffer.

100 µl of a dilution of the intestinal disaccharidase complex in 0.1 M maleate buffer, pH 6.25, are added to 10 µl of a sample solution, which is prepared such that the extinction of the test batch is at least 10%, but not more than 25%, below that of the 100% value, and the mixture is pre-incubated at 37°C for 10 minutes. The dilution of the disaccharidase complex should be adjusted to an activity of 0.1 SU/ml.

The saccharolytic reaction is started by adding 100 µl of a 0.4 M solution of sucrose ("SERVA 35579") in 0.1 M maleate buffer, pH 6.25, and, after an incubation period of 20 minutes at 37°C, is stopped by adding 1 ml of glucose dehydrogenase reagent (1 small bottle of lyophilised glucose dehydrogenase/mutarotase mixture ("MERCK 14053") and 331.7 mg of β-nicotinamide-adenine dinucleotide (free acid, "BOEHRINGER" degree of purity I) dissolved in 250 ml of 0.5 M tris buffer, pH 7.6). In order to determine the glucose, the mixture is incubated at 37°C for 30 minutes and finally is measured photometrically at 340 nm against a reagent blank (containing enzyme but without sucrose).

The calculation of the inhibitory activity of inhibitors is made difficult by the fact that even slight changes in the test system, for example a 100% value which varies slightly from determination to determination, have an effect on the test result which can no longer be ignored. These difficulties are avoided by running a standard with every determination; a saccharase inhibitor of the formula $C_{25}H_{43}O_{18}N$ which has a specific inhibitory activity of 77,700 SIU/g and, when employed in the test in amounts of 10 to 20 ng, leads to an inhibition of the order of size specified above, is used as the standard. If the difference between the extinctions at 340 nm of the 100%

value and of the batch inhibited by the standard is known, the specific inhibitory activity of the inhibitor, expressed in saccharase inhibitor units per gram (SIU/g), can be calculated in a known manner from the extinction difference between the 100% value and the batch inhibited by the sample solution, taking into consideration the amount of inhibitor employed.

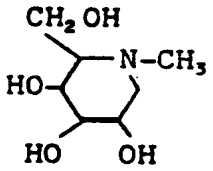
Specific saccharase-inhibitory activity in vitro

1-Desoxynojirimycin	465,000 SIU/g
N-Methyl-1-desoxynojirimycin	2,330,000 SIU/g

Preparation Examples

Example 1:

N-Methyl-1-desoxynojirimycin



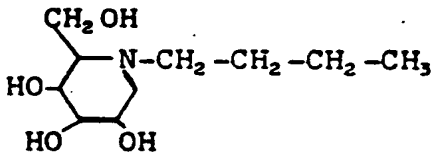
3.2 g of 1-desoxynojirimycin and 2 ml of 30% strength aqueous formaldehyde are added to 4 ml of 98% strength formic acid, whilst cooling with ice. The mixture is then heated under reflux for 8 hours. After cooling, the reaction mixture is diluted with acetone. A resinous precipitate separates out. The acetone solution is decanted off and the resin is rinsed several times with acetone. The residue is then dissolved in distilled water and the solution is freed from formic acid by adding a basic ion exchanger in the $^{\ominus}OH$ form (Amberlite JRA 410). The ion exchanger is filtered off and the aqueous solution is brought to dryness under reduced pressure. 3.0 g of resinous N-methyl-1-desoxynojirimycin remain. The compound can be further purified by chromatography on cellulose. Water-containing butanol is used as the running agent.

Mass spectrum: The most important peak in the upper mass range is at m/e = 146 ($M-CH_2OH$).

For further characterisation, the compound is converted into the peracetylated compound, N-methyl-2,3,4,6-tetra-O-acetyl-1-deoxynojirimycin, with acetic anhydride/pyridine 1:1 at room temperature. A proton magnetic resonance spectrum of this derivative in $CDCl_3$ was measured at 100 MHz:
4 singlets for the total of 12 protons, which correspond to the methyl groups of the O-acetyl groups ($\underline{CH_3}$-O-C(=O)-), are found between δ = 2.0 and 2.1 ppm. The methyl group bonded to N ($\underline{CH_3}$-N$\lessgtr$) is found as a singlet at δ = 2.45 ppm. Two protons on a C atom bonded to nitrogen (H-$\underline{\dot{C}}$-N$\lessgtr$) absorb as poorly resolved multiplets between δ = 2.1 and 2.5 ppm. A further proton of this type appears as a doublet of a doublet (J_1 = 11 Hz; J_2 = 4 Hz) at δ = 3.18 ppm. A methylene group (-$\underline{CH_2}$-O-C(=O)-CH_3) absorbs as an AB system at δ = 4.16 and δ = 4.22 ppm. The remaining three protons (-$\underline{\dot{C}}$-O-C(=O)-CH_3) are found as a multiplet between δ = 4.9 and 5.2 ppm.

Example 2:

N-n-Butyl-1-desoxynojirimycin



12.5 ml of n-butyraldehyde, 0.01 mols of methanolic HCl and 1.5 g of $NaCNBH_3$ are added successively to 3.2 g of 1-desoxynojirimycin (0.02 mol) in 40 ml of absolute methanol, whilst cooling with ice and stirring. The reaction mixture

is stirred at room temperature for 12 hours. It is then concentrated to dryness on a rotary evaporator. The residue is dissolved in 50 ml of water and extracted 3 times with 30 ml of $CHCl_3$ each time. The aqueous phase is again brought to dryness, the residue is taken up in 30 ml of H_2O and the solution is discharged onto a column 50 cm long and 2 cm wide which is filled with a strongly basic ion exchanger in the $OH^{\ominus}$ form (Amberlite IRA 400 or Dowex 1 x 2).

The reaction product is eluted with water and the individual fractions are investigated by thin layer chromatography. (Silica gel plates; running agent: ethyl acetate/methanol/water/25% strength ammonia 100:60:40:2; spray reagent: $KMnO_4$ solution). The fractions which contain N-n-butyl-1-desoxynojirimycin are collected and the aqueous solution is concentrated on a fractionating evaporator. Acetone is added to the residue, whereupon crystallisation occurs.

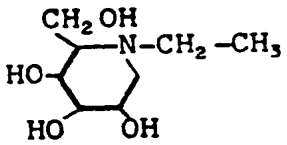
The crystals are filtered off, rinsed briefly with acetone and dried. 3 g of N-n-butyl-1-desoxynojirimycin of melting point 126-127°C are obtained.

Mass spectrum: The most important peaks in the upper mass range are found at m/e = 188 ($M-CH_2OH$) and m/e = 176 ($M-CH_2-CH_2-CH_3$).

In the case of less reactive aldehydes, a molecular sieve 3Å was added to the reaction mixture in order to bind the water of reaction.

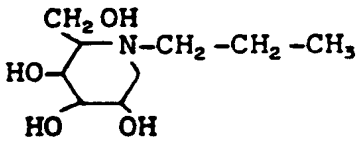
The following compounds were prepared analogously to these instructions:

N-Ethyl-1-desoxynojirimycin



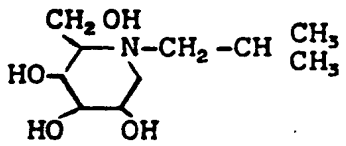
Mass spectrum: Intense peak at m/e = 160 ($M-CH_2OH$).

N-n-Propyl-1-desoxyjojirimycin



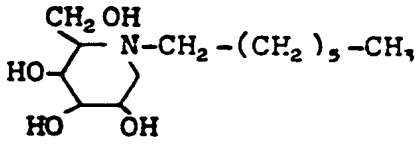
Mass spectrum: Intense peak at m/e = 174 ($M-CH_2OH$). Peaks also at m/e = 206 (M+H) and m/e = 204 (M-H).

N-iso-Butyl-1-desoxynojirimycin



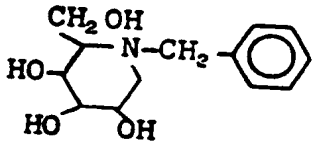
Mass spectrum: The most important peaks in the upper mass range are found at m/e = 188 ($M-CH_2OH$), m/e = 176 (m-$CH(CH_3)_2$), m/e = 220 (M+H) and m/e = 218 (M-H).

N-n-Heptyl-1-desoxynojirimycin



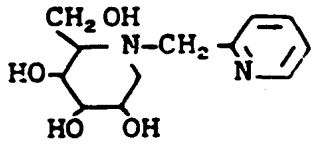
Mass spectrum: The most important peak in the upper mass range is at m/e = 230 ($M-CH_2OH$). Peaks are also found at m/e = 262 (M+H) and 260 (M-H).

N-Benzyl-1-desoxynojirimycin



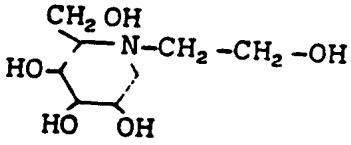
Mass spectrum: The most important peak in the upper mass range is found at m/e = 222 ($M-CH_2OH$).

N-(2-Pyridyl)-methyl-1-desoxynojirimycin



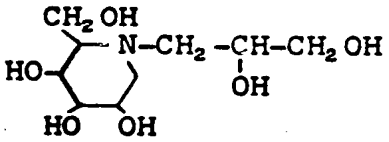
Mass spectrum: The most important peaks in the upper mass range are found at m/e = 255 (M+H), m/e = 236 ($M-H_2O$) and m/e = 223 ($M-CH_2OH$).

N-2-Hydroxyethyl-1-desoxynojirimycin



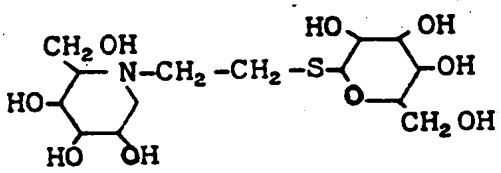
Mass spectrum: The most important peak in the upper mass range is at m/e = 176 ($M-CH_2OH$).

N-2,3-Dihydroxy-n-propyl-1-desoxynojirimycin



Mass spectrum: The most important peaks in the upper mass range are at m/e = 206 ($M-CH_2OH$) and m/e = 176. The substance is a mixture of two diastereomeric compounds.

N-(S-β-D-Glucopyranosyl-2-mercaptoethyl)-1-desoxynojirimycin

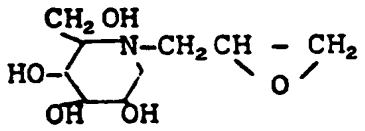


Mass spectrum: The mass spectrum of the compound peracetylated in pyridine/acetic anhydride was measured. The most important peaks in the upper mass range are found at m/e = 648

($M-CH_2O-\overset{\overset{O}{\|}}{C}-CH_3$), m/e = 588 and m/e = 344.

The aldehyde required for the reaction was obtained from O-acetylated 1-thioglucose and chloroacetaldehyde. The acetyl groups in the end product were split off by transesterification with catalytic amounts of $NaOCH_3$ in MeOH.

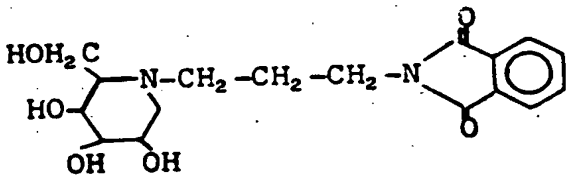
N-Oxiranyl-methyl-1-desoxynojirimycin



Mass spectrum: The most important peaks in the upper mass range are found at m/e = 219 (M), m/e = 202, m/e = 188 ($M-CH_2OH$) and m/e = 176 ($M-CH-CH_2$, O).

The substance is a mixture of two diastereomeric compounds.

N-(3-N-Phthalimido-n-propyl)-1-desoxynojirimycin

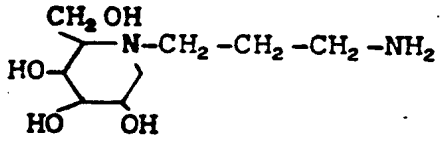


Mass spectrum: The most important peaks in the upper mass range were found at m/e = 348, m/e = 319 ($M-CH_2OH$), m/e = 301, m/e = 200, m/e = 188, m/e = 174, m/e 160 and m/e = 147.

In this case, chromatography on a basic ion exchanger was dispensed with and the compound was purified by boiling up with acetone and recrystallisation from ethanol.

Melting point : 208-210°C.

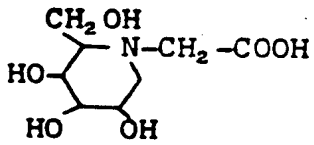
N-(3-Amino-n-propyl)-1-desoxynojirimycin



Mass spectrum: The most important peaks in the upper mass range are at m/e = 189 ($M-CH_2OH$) and m/e = 146.

The compound was obtained from the above phthalimido compound by hydrazinolysis in methanol.

N-(1-Desoxynojirimycin-yl)-acetic acid

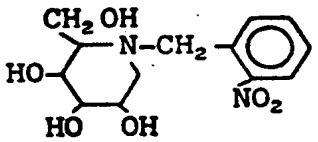


Mass spectrum: The most important peaks in the upper mass range are found at m/e = 203 ($M-H_2O$), m/e = 159, m/e = 145 and m/e = 100.

The compound was not purified by chromatography over a basic exchanger but by recrystallisation from methanol/water.

Melting point: 187-188°C.

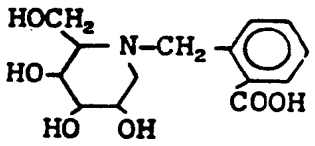
N-o-Nitrobenzyl-1-desoxynojirimycin



Rf value: 0.85 (on thin layer chromatography ready-to-use silica gel 60 plates from Messrs. Merck; running agent: ethyl acetate/methanol/H_2O/25% strength ammonia 100:60:40:2).

For comparison: Rf value of 1-desoxynojirimycin : 0.3.

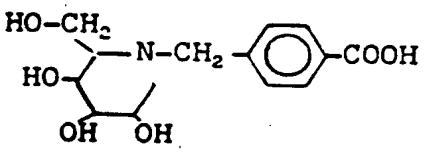
N-o-Carboxybenzyl-1-desoxynojirimycin



Rf value : 0.7 (plates and running agent as indicated for the above compound).

For purification, the compound was chromatographed over a basic as indicated above, but finally was eluted with 1% strength acetic acid.

N-p-Carboxybenzyl-1-desoxynojirimycin



Rf value : 0.7 (plates and running agent as indicated above).

In this case also, the compound was eluted from the basic exchanger with 1% strength acetic acid.